DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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WARNING LETTER

VIA REGISTERED MAIL

WL No. 320-01-14

October 2, 2001

Mr. Jing Bin
Vice President
Northeast General Pharmaceutical Factory
No. 37 Zhonggong Bei Street
TIEXI, SHENYANG 110026
Peoples Republic of China

Dear Mr. Jing:

This is regarding an inspection of your active pharmaceutical ingredient (API) manufacturing facility in Shenyang, PRC, by FDA Investigator, John D. White, and Chemist, Dr. S. Nasir Ali, during May 28 - June 1, 2001. The inspection revealed significant deficiencies in the manufacture of bulk Sucralfate U.S.P. that resulted in the issuance of 16-item FDA Form 483 at the completion of the inspection.

These deviations cause this API to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act which requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practice (CGMP). No distinction is made between active pharmaceutical ingredients and finished pharmaceuticals, and failure of either to comply with CGMP constitutes a failure to comply with the requirements of the Act.

We have reviewed your June 15, 2001 response to the FDA-483 observations and concluded that your response lacks sufficient details, explanations, and time commitments to address all the deviations adequately. Specific areas of concern include:

1. Stability samples for Sucralfate batch numbers DY96-04-003, 005, and 0028 that were tested to provide stability data for the DMF amendment 97-001 were not traceable to the batches produced at the manufacturing site. Data submitted in the amendment is different from data obtained for the release of these batches. The reason why the stability studies for these batches were terminated after six months could not be satisfactorily explained.

During the inspection of your facility, you were unable to present records of raw data pertaining to the subject stability batches submitted as part of 97-amendment for DMF-7552 or provide complete shipping records documenting that stability samples were shipped to your US

contract test laboratory. Additionally, you were unable to provide us with the status of your stability studies beyond six months.

Your FDA-483 response stated that your contract laboratory, Pharmaceutical International Inc (PII.), Hunt Valley, Maryland, had continued the stability study on the subject stability batches at 9, 12, 18, 24, and 43 month time intervals. Your response is inadequate in that you did not present copies of the shipping records to demonstrate that you shipped the subject stability batches to your contract laboratory, PII, and did not present copies of the raw data (including chromatograms) in support of the additional stability data that you submitted in the DMF.

2. Analysis for sucralfate assay and related compounds and limit tests for pyridine and 2-methylpyridine in sucralfate were not performed according to the USP method stated in the DMF and did not establish that the alternate method is as good or better than the USP method. Additionally, analysts were using sample injections instead of standard injections to demonstrate system suitability. The potassium sucrose octasulfate secondary reference standard used, as part of release and testing protocols, was not qualified against USP potassium sucrose octasulfate standard.

Your response commits to adopt the USP method, purchase and use USP potassium sucrose octasulfate standard to calibrate your secondary standard, and use standard injections to demonstrate system suitability. However, your response is inadequate in that it failed to document that these corrective actions have been implemented or provide a reasonable time frame for implementation.

3. The calibration procedure for HPLC systems is inadequate in that it did not include integrator and detector's linearity, injector's reproducibility, and accuracy of temperature settings for column heater and detector. The calibration procedure for GC systems is also inadequate as it did not address calibration of flow rates, accuracy of temperature settings for column and injection port temperature, injector's reproducibility, and detector's linearity. Additionally, temperature and flowrate calibration checks were not performed on GC headspace unit.

CGMP requires that you calibrate test instruments at suitable intervals in accordance with established written procedures and that instruments not meeting established specifications shall not be used.

Your response commits to correcting these deficiencies by entrusting the biannual calibration responsibility to the State Measurement Institute and to submit the report of corrective action through your annual report for sucralfate. We would like to remind you that although State Measurement Institute performs the calibrations, you would have the responsibility to make sure that it is using appropriate procedures and adequate equipment and facilities and that the data are reliable. Your standard operating procedures should be revised appropriately to reflect the proposed changes. This is a significant deficiency and it warrants immediate corrective action and reporting from your firm.

4. Calibration raw data and results obtained for the performance qualification of analytical instruments is not being checked for accuracy and completeness by a second analyst or

laboratory supervisor. Additionally, for routine sample analyses, analysts were not adequately recording the raw analytical data in their notebooks. For example, review of Sucralfate release data for batch #DY99-10-0014 revealed that no raw data were recorded in the notebooks for identification tests B & C; aluminum, arsenic, and heavy metal tests.

Your response to this deficiency is inadequate in that it did not include a standard operating procedure detailing how you intend to control the distribution and use of laboratory notebook sheets.

The CGMP deviations identified above or the FDA-483 issued to you are not to be considered as an all-inclusive list of deficiencies at this facility. FDA inspections are audits, which are not intended to determine all deviations from CGMPs that exist at a firm. If you wish to continue to ship bulk drug products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for current good manufacturing practices.

Please respond to this letter and provide a status report on the ongoing corrective actions within 30 days. Until FDA has reinspected this facility and confirms compliance with CGMPs and correction of these deficiencies, this office will recommend withholding approval of any new drug applications listing this facility as the manufacturer of active pharmaceutical ingredients (APIs). Failure to promptly correct these deficiencies may result in the refusal to permit entry of these products into the United States.

Please direct your written response to Compliance Officer Muralidhara Gavini at the address shown below. Please reference CFN# 9614298 within your response.

U.S. Food & Drug Administration
CDER HFD-322
7520 Standish Place
Rockville, MD 20855-2737
Tel: (301) 594-0095; FAX (301) 594-1033

To schedule a reinspection of this facility after corrections have been completed and it is in compliance with CGMPs, contact: Director, International Drug Section, HFC-133, Division of Emergency and Investigational Operations, 5600 Fishers Lane, Rockville, MD 20857, Tel. (301) 827-5655 or FAX (301) 443-6919.

Sincerely,

Joseph C. Famulare
Director
Division of Manufacturing & Product Quality
Center for Drug Evaluation & Research

CC: Mr. Paul Sudhakar, President, Martec Pharmaceuticals, Inc. Fax #800-287-7576